Aldehyde dehydrogenase 2—a potential genetic risk factor for lung function among southern Chinese: evidence from the Guangzhou Biobank Cohort Study

Au Yeung, Shiu Lun; Jiang, Chaoqiang; Cheng, Kar Keung; Adab, Peymane; Lam, Kin Bong Hubert; Liu, Bin; Zhang, Weisen; Lam, Tai Hing; Leung, Gabriel Matthew; Schooling, Catherine Mary

DOI:
10.1016/j.annepidem.2014.05.015

Accepted Manuscript

Aldehyde dehydrogenase 2 - a potential genetic risk factor for lung function among Southern Chinese from the Guangzhou Biobank Cohort Study

Shiu Lun Au Yeung , PhD Chaoqiang Jiang , MD Kar Keung Cheng , PhD Peymane Adab , MD Kin Bong Lam , PhD Bin Liu , PhD Weisen Zhang , MD Tai Hing Lam , MD Gabriel Matthew Leung , MD C Mary Schooling , PhD

PII: S1047-2797(14)00196-3

DOI: 10.1016/j.annepidem.2014.05.015

Reference: AEP 7665

To appear in: *Annals of Epidemiology*

Received Date: 25 February 2014

Revised Date: 26 May 2014

Accepted Date: 30 May 2014

Please cite this article as: Au Yeung SL, Jiang C, Cheng KK, Adab P, Lam KB, Liu B, Zhang W, Lam TH, Leung GM, Schooling CM, Aldehyde dehydrogenase 2 - a potential genetic risk factor for lung function among Southern Chinese from the Guangzhou Biobank Cohort Study, *Annals of Epidemiology* (2014), doi: 10.1016/j.annepidem.2014.05.015.

Type of article: Original Article

Aldehyde dehydrogenase 2 - a potential genetic risk factor for lung function among Southern Chinese from the Guangzhou Biobank Cohort Study

SHIU LUN AU YEUNG, PhD [1], CHAOQIANG JIANG, MD[2], KAR KEUNG CHENG, PhD[3], PEYMANE ADAB, MD[3], KIN BONG LAM, PhD[4], BIN LIU, PhD[2], WEISEN ZHANG, MD[2], TAI HING LAM, MD[1]†, GABRIEL MATTHEW LEUNG, MD[1], C MARY SCHOOLING, PhD[1,5]

[1]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China, [2]Guangzhou No. 12 Hospital, Guangzhou, Guangdong, China, [3]Department of Public Health and Epidemiology, University of Birmingham, Birmingham, UK, [4]Institute of Occupational and Environmental Medicine, University of Birmingham, Birmingham, UK and, [5]CUNY School of Public Health, Hunter College, New York, NY, USA

†Corresponding author:

Prof TH Lam
School of Public Health
The University of Hong Kong
5/F William MW Mong Block
Faculty of Medicine Building
21 Sassoon Road, Hong Kong
Fax: (852) 2855 9528
E-mail: hrmrlth@hkucc.hku.hk

Word count

Abstract: 200

Total word count: 2,999

Tables: 4

Keywords: Southern Chinese; Aldehyde dehydrogenase 2; lung function

ABSTRACT

Purpose: In Asia moderate alcohol users have better lung function. Never users have more inactive aldehyde dehydrogenase 2 (*ALDH2*) alleles (A) potentially generating confounding, because inactive alleles may increase acetaldehyde exposure and reduce lung function.

Methods: We examined the association of *ALDH2* genotypes with percentage predicted lung function (forced expiratory volume in 1 second (FEV_1); forced vital capacity (FVC)) for age, sex and height among 5,641 older Chinese using multivariable linear regression.

Results: *ALDH2* genotypes were associated with alcohol use and height but not other attributes. Inactive alleles were inversely associated with lung function (% predicted FEV_1 -1.52%, 95% confidence interval (CI) -2.52% to -0.51% for one inactive allele and -2.05%, 95% CI -3.85% to -0.26% for two inactive alleles compared to two active alleles; and for % predicted FVC -1.25%, 95% CI -2.15% to -0.35% and -1.65%, 95% CI -3.25% to -0.04%). The association of moderate use with lung function was attenuated after adjusting for *ALDH2*, in addition to other potential confounders.

Conclusions: Previous findings in Chinese may be confounded by *ALDH2*. High frequency of inactive *ALDH2* alleles in East Asia may exacerbate the effect of environmental acetaldehyde exposure on lung function, and potentially on chronic obstructive pulmonary disease.

List of abbreviations

AIC: Akaike Information Criterion

ALDH2: Aldehyde dehydrogenase 2

CI: Confidence Interval

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

GBCS: Guangzhou Biobank Cohort Study

GHHARE: The Guangzhou Health and Happiness Association for the Respectable Elders

GWAS: Genome wide association study

HEPA Health-enhancing physical activity

IPAQ International Physical Activity Questionnaire

MET metabolic equivalent

SD Standard deviation

SNP: Single nucleotide polymorphism

Introduction

Moderate alcohol use is associated with better lung function in western populations (1, 2), potentially via alcohol's effect on bronchodilation (3). However, this association is difficult to interpret because moderate alcohol users in western populations tend to have more healthy attributes than never users (4). Replication of these findings in a setting with a different social patterning of alcohol use, such as among Chinese (5), is one way to assess if associations seen in western studies are biologically based or a contextually specific artifact of confounding. In Chinese settings alcohol use is also associated with better lung function and lower mortality from chronic obstructive pulmonary disease (6-9), suggesting the associations seen may be generic. However, the positive association is more evident in men than women (6, 8) and adjustment for potential confounders, such as socio-economic position and lifestyle, fail to explain these sex differences (6, 8). Such differences may imply the existence of a sex-linked factor which modifies the association of alcohol use with lung function, or more parsimoniously may indicate confounding (10).

In contrast to western populations, patterns of alcohol use in Chinese populations are also influenced by aldehyde dehydrogenase 2 (*ALDH2*) genotype (11, 12). *ALDH2* is largely monomorphic in western populations but polymorphic in East Asian populations including Chinese (13). Inactive *ALDH2* allele (A) carriers metabolize the first metabolite of alcohol,

acetaldehyde, less effectively than active allele (G) carriers, so they are more likely to flush and generally feel unwell in response to alcohol use and so drink less (11). Among southern Chinese men *ALDH2* genotype may determine alcohol use, but southern Chinese women generally refrain from alcohol use, according to traditional social norms, regardless of genotype (14). Alcohol use thus corresponds to *ALDH2* genotype more among men than women in southern Chinese populations. We have previously hypothesized that the observed positive association of alcohol use with respiratory health in Chinese men might be due to *ALDH2* genotype affecting both alcohol use and lung function rather than to alcohol use itself (8), because of generally greater acetaldehyde exposure in people with inactive *ALDH2* alleles detrimentally affecting lung function, so that the observed association could be due to genetic confounding (8). To test this hypothesis, first we examined whether *ALDH2* was associated with lung function among older Southern Chinese in the Guangzhou Biobank Cohort Study, and second whether the association of moderate alcohol use with lung function was confounded by *ALDH2* genotype.

Methods

Ethics statement

The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent before participation.

Participants

The Guangzhou Biobank Cohort Study (GBCS) is a collaboration between the Guangzhou No.12 Hospital and the Universities of Hong Kong and Birmingham (15). Recruitment of participants draws from "The Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE)", a community social and welfare association unofficially aligned with the municipal government where membership is open to anyone aged 50 years or older for a monthly, nominal fee of 4 Yuan (50 US cents). There were three recruitment phases. Recruitment for phase 1 took place from September 2003 to November 2004, phase 2 from April 2005 to May 2006, and phase 3 from September 2006 to January 2008. Follow-up of the participants started in 2008. Approximately 7% of permanent Guangzhou residents aged 50 years or more are members of GHHARE, of whom 33% enrolled for phases 1, 2 or 3 and were included if they were capable of consenting, ambulatory, and not receiving treatment modalities that, if omitted, may result in immediate life-threatening risk, such as chemotherapy or radiotherapy for cancer, or dialysis for renal failure. Participants in GBCS are ethnic Chinese largely from southern China. Participants underwent a detailed interview and physical examination at baseline recruitment, including lifestyle, medical history and spirometry. Spirometry utilising a pneumotachograph (Chestgraph HI-701, Chest MI Inc, Tokyo, Japan) in phase 1, a turbine flowmeter (Cosmed microQuark, Rome, Italy) in phase 2,

and an ultrasound flowmeter (ndd Easy on-PC, Zurich, Switzerland) in phase 3 followed a detailed protocol with quality assurance as described previously (16). In brief, at least three manoeuvres were performed without the use of bronchodilator with the best measure of forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) recorded.

DNA extraction and Single Nucleotide Polymorphism (SNP) analysis

Biological samples for DNA extraction used in the present study were obtained in GBCS phase 3 at recruitment and in phases 1 and 2 at follow-up. DNA was extracted at Guangzhou No. 12 Hospital either from fresh blood using a standard phenol-chloroform extraction procedure and stored at -80°C or from blood or buffy coat previously stored at -80°C using a standard magnetic bead extraction procedure (17). Genotyping was performed using the MassARRAY system (Sequenom, San Diego, CA, USA) and the iPLEX assay at a commercial company (Beijing CapitalBio Corporation, Beijing, China).

Exposures

ALDH2.

The *ALDH2* genotypes (AA, GA or GG) were identified from SNP rs671.

Alcohol use

To reflect patterns of alcohol use in our setting, we categorized alcohol use as never, occasional, moderate, heavy and former drinker, based on the frequency of alcohol use and the usual amount per occasion, as described previously (18). In brief, occasional alcohol users were people who consumed alcohol less than once a week, often only once or twice a year; moderate alcohol users were defined as people using alcohol weekly with average consumption ≤140g ethanol per week for women and ≤210g for men. Heavy drinkers were people using alcohol weekly and consuming more than those amounts.

Outcomes

The outcomes were percentage (%) predicted FEV_1 and % predicted FVC obtained from validated prediction equations based on age, sex and height developed for Southern Chinese (19). Percentage predicted values take into account variation due to age, sex and height; they were used for consistency with previous studies (16, 20).

Statistical analysis

We tested for Hardy-Weinberg equilibrium at the SNP locus on a contingency table of observed-versus-predicted frequencies with an exact test. We used analysis of variance (ANOVA) and chi square tests to examine for any differences in height, socioeconomic position or lifestyle by *ALDH2* genotypes. We used multivariable linear regression to

examine the adjusted associations of *ALDH2* genotypes and alcohol use with percentage predicted lung function. We assessed P for trend using *ALDH2* genotypes as a continuous variable. We examined whether the associations of *ALDH2* or alcohol use with % predicted lung function varied by sex from heterogeneity across strata and the P-value of the relevant interaction term. For the association of *ALDH2* with % predicted lung function, model 1 was unadjusted, and model 2 was additionally adjusted for recruitment phase, alcohol use, to control for mediation by alcohol use, socio-economic position (education and longest-held occupation) and lifestyle (smoking, secondhand smoke exposure at home (cohabited with a smoker) and at work (indoor) and physical activity), to control for collider bias when adjusting for alcohol use (as alcohol use is a common effect of *ALDH2* and factors confounding the association of alcohol use and lung function). For the association of alcohol use with % predicted lung function, model 1 was adjusted for socio-economic position, lifestyle, and recruitment phase. Model 2 was additionally adjusted for *ALDH2*. We tested whether *ALDH2* improved model fit using the Akaike Information Criterion (AIC), where a lower AIC indicates a better fitting model. Alcohol use is uncommon in older southern Chinese women. Therefore, we assessed the possibility that any apparent genetic associations were an artifact, of residual mediation from adjustment by less than perfectly measured alcohol use, by performing sex stratified analyses to examine if the associations were consistent by sex. We also similarly examined whether the associations of alcohol use with %

predicted lung function varied by sex. Finally, we repeated the analyses using raw lung function adjusted for age, sex and height as a sensitivity analyses.

All statistical analyses were conducted using Stata version 10.1 (StataCorp LP, College Station, TX).

Results

Out of 30,499 participants in GBCS, 9152 (30%) had valid *ALDH2* genotype assessed with availability depending on logistics and the demands of other projects. Of these, 5,641 had complete information on % predicted lung function, alcohol use and other covariates, exclusions were mainly due to invalid lung function measurements. *ALDH2* genotypes had a distribution consistent with Hardy-Weinberg equilibrium (P=0.88).

About half the men (48%) were never alcohol users, 28% occasional users, 11% moderate users, 7% heavy users and 6% formers users; 63% of women were never users, 29% occasional users, 3% moderate, 0.4% heavy and 4% former users. Moderate alcohol use is associated with a slightly lower socio-economic position and less healthy lifestyle among men but not women in this study (21). Mean % predicted FEV_1 was 94.4% and FVC 93.4%. Table 1 shows that men with more inactive alleles (A) were more likely to be non-alcohol

users and to be shorter, but *ALDH2* genotypes were not associated with age, education, longest held occupation, smoking, secondhand smoke exposure or physical activity. Table 2 shows similar patterns for women. Inactive allele carriers appeared less likely to be physically inactive although no clear linear trend was observed. FEV_1 and FVC were positively associated with active *ALDH2* alleles.

(Tables 1, 2 here)

Overall inactive *ALDH2* alleles (A) were associated with lower % predicted FEV_1 and FVC (Model 1, Table 3). Additional adjustment for recruitment phase, alcohol use, socio-economic position, smoking, secondhand smoke exposure and physical activity did not fully explain the genetic associations (Model 2). The association of *ALDH2* with % predicted lung function did not vary by sex. In sex stratified analysis, the genetic associations with % predicted lung function were qualitatively similar in men and women.

(Table 3 here)

Overall, moderate and occasional alcohol users had higher % predicted FEV_1 and % predicted FVC whereas heavy users only had higher % predicted FEV_1 (Table 4 model 1). Additional adjustment for *ALDH2* genotypes, in Model 2, attenuated some associations, so moderate alcohol use was no longer associated with % predicted lung function. Moreover, the

model including *ALDH2* had a lower AIC indicating a better fit. The associations of alcohol use with % predicted lung function did not vary by sex. However, in sex stratified analysis, moderate use remained associated with higher lung function in women in model 2 adjusting for confounders and *ALDH2*. Using raw lung function adjusted for age, sex and height in all analyses gave similar results (data not shown).

(Table 4 here)

Discussion

Carriers of *ALDH2* inactive allele (A) had lower % predicted FEV_1 and % predicted FVC. These genetic associations were not explained by socio-economic position, smoking or alcohol use. To our knowledge, this is the first study to show that *ALDH2* is a potential genetic risk factor for poorer lung function. We also found occasional and moderate alcohol use associated with higher % predicted lung function, consistent with previous studies (1, 6). However, further adjustment for *ALDH2* attenuated these associations. In particular, moderate alcohol users no longer had higher % predicted lung function after adjustment for *ALDH2*. Our study adds by suggesting that previous studies showing a potential protective effect of moderate alcohol use on lung function among Chinese may be confounded by *ALDH2*. The inconsistent result between our study and previous western studies suggests better lung

function observed in moderate alcohol users in previous studies could be due to confounding by socio-economic position and lifestyle.

Acetaldehyde accumulation is associated with poorer lung function (22). Building on the enzymatic role of *ALDH2,* Schooling et.al. previously hypothesized that inactive *ALDH2* alleles could have a detrimental impact on lung function because of generally greater acetaldehyde exposure due to slower acetaldehyde metabolism (8), Cigarette smoke is a possible source of acetaldehyde exposure. Lung function was poorer among smokers with more inactive *ALDH2* alleles (data not shown), as would also be expected, possibly due to greater acetaldehyde exposure. Another possible source of acetaldehyde exposure is air pollution (23). As air pollution is common, *ALDH2* genetic polymorphisms, a modifier of the effect of air pollution on lung function via varying metabolization rates of acetaldehyde, will appear to be a risk factor (24). Consistent with this hypothesis we found inactive *ALDH2* alleles associated with poorer predicted % lung function. If this hypothesis holds, it implies that people with inactive *ALDH2* alleles, such as in East Asian populations, could be more prone to the detrimental effects of air pollution, air quality in the region is deteriorating (25), and may intensify the burden of diseases associated with reduced lung function. Nevertheless, other possible explanations for our findings exist. Inactive *ALDH2* alleles were associated with greater height (Tables 1 and 2), which affects lung function. However, the association of

ALDH2 was evident for sex-specific, age and height standardized % predicted lung function. Genome wide association studies (GWAS) have not identified *ALDH2* as associated with lung function (26, 27), however these studies mainly concerned people of European ancestry where *ALDH2* is monomorphic (13). Alternatively, genetic variants in linkage disequilibrium with *ALDH2* or pleiotropic effects of *ALDH2*, by some as yet unknown but biologically plausible, pathway could explain this association. For example, *ALDH2* polymorphism may modify the effect of air pollution on lung growth in childhood, and lead to the differences in lung function by *ALDH2* genotypes in later life (28). *ALDH2* also has enzymatic functions (dehydrogenase and nitrate reductase) related to oxidative stress (29, 30) which may also contribute to differences in lung function by *ALDH2* genotype (31).

On the other hand, the use of a setting with different social patterning of alcohol use to verify associations in studies where there are marked differences in health attributes among alcohol users is an alternative way to verify whether these associations are due to residual confounding when randomized controlled trials are not feasible (5). Previous East Asian studies showing positive associations of moderate alcohol use with lung function did not control for *ALDH2* (6, 8), which may be a potential confounder in Asian populations. The lack of consistency between our study and previous western studies may also imply that previous studies (1, 2) could be confounded by healthier attributes among moderate users.

Smoking and alcohol use often occur together. The association of alcohol use with lung function could be confounded by smoking. However, we adjusted for smoking (Table 4, model 1) and the associations did not differ by smoking status (data not shown). Although moderate users had higher lung function after adjusting for confounders and *ALDH2* among women, the possibility of residual confounding could not be ruled out as alcohol use among women was uncommon, making confounder adjustment inefficient. Similarly, we found occasional alcohol use (drinking less than once per week) consistently associated with higher % predicted lung function despite alcohol use at a low level unlikely to have any biological effects (Table 4). These positive associations are likely an artifact of residual and uncontrolled confounding by healthier attributes among occasional users, as described elsewhere (5). At older ages an association of heavy alcohol use with health may also be due to confounding, specifically by ill-health, as heavy drinkers made ill by alcohol may have quit drinking or reduced their alcohol intake, thereby generating a spurious association of heavy alcohol use with better health.

Although this is the first study to suggest *ALDH2* as a potential determinant of lung function in a large Chinese sample and to assess its confounding of the association of alcohol use with lung function, limitations exist. First, alcohol use is notoriously difficult to assess precisely. The observed associations of *ALDH2* with lung function could be due to residual mediation

by alcohol use, which may affect lung function (3), although not evident in our study. However, alcohol use is low among women and the associations were similar by sex. Second, the % change in lung function by *ALDH2* genotypes was only 1-2%. This effect size may not be clinically relevant. Nevertheless, such a shift in lung function at the population level could from a public health perspective have significant implications for the burden of diseases associated with lung function and could be relevant to the differences in chronic obstructive pulmonary disease mortality rates between populations with different distributions of *ALDH2* genotypes. Third, although this was a hypothesis driven study, it was not a GWAS; we know of no large GWAS studies of lung function in East Asians. A GWAS of lung function in East Asians would be valuable to confirm or refute whether *ALDH2* is a risk factor for lung function in Asians. Fourth, GBCS is not population representative. Our findings would be biased if the study had selectively excluded people who were inactive *ALDH2* allele carriers and had better lung function or who were moderate alcohol users with poor lung function, which is unlikely (32). The *ALDH2* allele frequency and its relationship with alcohol use are similar to previous studies (11, 33). More importantly, GBCS comprises of permanent residents (i.e. with residence registration) of Guangzhou, capital of Guangdong province, and most share a common Cantonese heritage (15). The geo-ethnic homogeneity of the samples in GBCS thus reduces the probability of confounding by population stratification (34). Similarly, differences in allele frequency by markers of socioeconomic position (Tables 1, 2) were not

evident suggesting little socio-economic confounding.

This study showed that inactive *ALDH2* alleles might be a potential risk factor for poor lung function in a Chinese population. The presence of *ALDH2* polymorphisms in Chinese, and other East Asian populations, may exacerbate any detrimental effect of environmental acetaldehyde exposure on lung function, with potential implications for chronic obstructive pulmonary disease in these settings. Moreover, this study showed that moderate alcohol use was not positively associated with lung function among Southern Chinese, after adjusting for *ALDH2* genotype. This suggests that the positive association of moderate alcohol use with lung function seen in previous East Asian studies could be a result of genetic confounding. Lastly, inconsistencies between our findings and those from the West may suggest that western observational studies are confounded by healthier attributes among moderate users, although larger studies are needed to verify our negative finding.

Financial support

This study was supported by the Hong Kong Health and Health Services Research Fund (grant no. 06070981), Health, Welfare and Food Bureau, Government of the Hong Kong SAR, People's Republic of China. The Guangzhou Biobank Cohort Study was funded by The University of Hong Kong Foundation for Development and Research, and the University of

Hong Kong University Research Committee Strategic Research Theme Public Health, Hong Kong; Guangzhou Public Health Bureau, and Guangzhou Science and Technology Bureau, Guangzhou, China; and The University of Birmingham, UK and the Natural Science Foundation of Guangdong (grant no. 9451062001003477), Guangdong, China. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgment

The Guangzhou Biobank Cohort Study investigators include: Guangzhou No. 12 Hospital: WS Zhang, M Cao, T Zhu, B Liu, CQ Jiang (Co-PI); The University of Hong Kong: CM Schooling, SM McGhee, R Fielding, GM Leung, TH Lam (Co-PI); The University of Birmingham: GN Thomas, P Adab, KK Cheng (Co-PI). We thank L Xu and T Zhu for facilitating the DNA extraction.

Conflict of interest

The authors have no conflict of interest, financial or otherwise.

References

1. Tabak C, Smit HA, Rasanen L, et al. Alcohol consumption in relation to 20-year COPD mortality and pulmonary function in middle-aged men from three European

countries. Epidemiology 2001;12(2):239-45.
2. Sisson JH, Stoner JA, Romberger DJ, et al. Alcohol intake is associated with altered pulmonary function. Alcohol 2005;36(1):19-30.
3. Sisson JH. Alcohol and airways function in health and disease. Alcohol 2007;41(5):293-307.
4. Naimi TS, Brown DW, Brewer RD, et al. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking US adults. Am J Prev Med 2005;28(4):369-73.
5. Au Yeung SL, Jiang C, Zhang W, et al. Systematic differences among never, occasional and moderate alcohol users in southern China, and its use in alcohol research: a cross-sectional study. J Epidemiol Commun H 2013.
6. Reilly KH, Gu D, Duan X, et al. Risk factors for chronic obstructive pulmonary disease mortality in Chinese adults. Am J Epidemiol 2008;167(8):998-1004.
7. Yang L, Zhou MG, Sherliker P, et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220 000 men with 15 years of follow-up. Int J Epidemiol 2012;41(4):1101-13.
8. Schooling CM, Lam TH, Ho SY, et al. Alcohol and cardio-respiratory deaths in Chinese: a population-based case-control study of 32,462 older Hong Kong adults. BMC Public Health 2009;9:-.
9. Shen C, Ni M, Schooling CM, et al. Alcohol use and death from respiratory disease in a prospective chinse elderly cohort study in Hong Kong. Prev Med 2013.
10. Petitti D. Commentary: hormone replacement therapy and coronary heart disease: four lessons. Int J Epidemiol 2004;33(3):461-3.
11. Muramatsu T, Wang ZC, Fang YR, et al. Alcohol and aldehyde dehydrogenase genotypes and drinking behavior of Chinese living in Shanghai. Hum Genet 1995;96(2):151-4.
12. Thomasson HR, Edenberg HJ, Crabb DW, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet 1991;48(4):677-81.
13. Goedde HW, Agarwal DP, Fritze G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 1992;88(3):344-6.
14. Chen L, Davey-Smith G, Harbord RM, et al. Alcohol intake and blood pressure: a systematic review implementing a Mendelian randomization approach. PLoS Med 2008;5(3):e52.
15. Jiang C, Thomas GN, Lam TH, et al. Cohort profile: The Guangzhou Biobank Cohort Study, a Guangzhou-Hong Kong-Birmingham collaboration. Int J Epidemiol 2006;35(4):844-52.
16. Yin P, Jiang CQ, Cheng KK, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet

2007;370(9589):751-7.

17. Au Yeung SL, Jiang CQ, Cheng KK, et al. Evaluation of Moderate Alcohol Use and Cognitive Function Among Men Using a Mendelian Randomization Design in the Guangzhou Biobank Cohort Study. Am J Epidemiol 2012;175(10):1021-8.
18. Schooling CM, Jiang CQ, Lam TH, et al. Alcohol use and fasting glucose in a developing southern Chinese population: the Guangzhou Biobank Cohort Study. J Epidemiol Commun H 2009;63(2):121-7.
19. Ip MS, Ko FW, Lau AC, et al. Updated spirometric reference values for adult Chinese in Hong Kong and implications on clinical utilization. Chest 2006;129(2):384-92.
20. Lam KB, Jordan RE, Jiang CQ, et al. Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study. Eur Respir J 2010;35(2):317-23.
21. Au Yeung SL, Jiang CQ, Zhang WS, et al. Systematic differences among never, occasional and moderate alcohol users in southern China, and its use in alcohol research: a cross-sectional study. J Epidemiol Commun H 2013;67(12):1054-60.
22. Matsuse H, Fukushima C, Shimoda T, et al. Effects of acetaldehyde on human airway constriction and inflammation. Novartis Foundation symposium 2007;285:97-106; discussion -9, 98-9.
23. United States Environmental Protection Agency. Acetaldehyde. (http://www.epa.gov/ttn/atw/hlthef/acetalde.html). (Accessed 16 December 2013).
24. Brotman DJ, Walker E, Lauer MS, et al. In search of fewer independent risk factors. Arch Intern Med 2005;165(2):138-45.
25. Alcorn T. China's skies: a complex recipe for pollution with no quick fix. Lancet 2013;381(9882):1973-4.
26. Soler Artigas M, Loth DW, Wain LV, et al. Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nature genetics 2011;43(11):1082-90.
27. Wilk JB, Chen TH, Gottlieb DJ, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet 2009;5(3):e1000429.
28. Schultz ES, Gruzieva O, Bellander T, et al. Traffic-related Air Pollution and Lung Function in Children at 8 Years of Age A Birth Cohort Study. Am J Resp Crit Care 2012;186(12):1286-91.
29. Daiber A, Munzel T. Nitrate reductase activity of mitochondrial aldehyde dehydrogenase (ALDH-2) as a redox sensor for cardiovascular oxidative stress. Methods Mol Biol 2010;594:43-55.
30. Chen CH, Sun L, Mochly-Rosen D. Mitochondrial aldehyde dehydrogenase and cardiac diseases. Cardiovascular research 2010;88(1):51-7.
31. Schunemann HJ, Muti P, Freudenheim JL, et al. Oxidative stress and lung function. Am J Epidemiol 1997;146(11):939-48.

32. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. Int J Epidemiol 2013;42(4):1012-4.
33. Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: A literature review. Alcohol Research & Health 2007;30(1):22-7.
34. Cardon LR, Palmer LJ. Population stratification and spurious allelic association. Lancet 2003;361(9357):598-604.

Table 1: Characteristics by Aldehyde Dehydrogenase 2 *(ALDH2)* Genotype Among 2,855 Older Southern Chinese Men From the Guangzhou Biobank Cohort Study

		ALDH2 genotype (from rs671)			
		Two active alleles (GG) (n=1420)	One active allele (GA) (n=1200)	No active allele (AA) (n=235)	[a]P value
FEV_1 (L)	Mean (SD)	2.36 (0.6)	2.30 (0.6)	2.26 (0.6)	0.009
FVC (L)	Mean (SD)	3.05 (0.6)	2.99 (0.7)	2.94 (0.6)	0.007
Height (cm)	Mean (SD)	164.8 (6.1)	164.3 (5.8)	163.5 (6.0)	0.003
Age group (%) years	50-54	11	11	12	0.22
	55-59	23	22	21	
	60-64	26	24	26	
	65-69	21	21	18	
	70-74	14	15	16	
	75-79	4	6	7	
	80+	2	1	0	
Education (%)	Less than primary	2	2	1	0.66
	Primary	26	28	25	
	Junior middle	31	30	33	
	Senior middle	24	25	26	
	Junior college	9	9	11	
	College	7	6	5	
[b]Longest held occupation (%)	Manual	54	58	57	0.17
	Non-manual	38	33	35	
	Others	8	9	8	
Smoking status (%)	Never	38	38	42	0.31
	Former	27	28	30	
	Current	35	34	28	
Secondhand smoke exposure at home (%)	Yes	20	23	19	0.17
Secondhand smoke exposure at indoor work (%)	Yes	75	75	76	0.87
Drinking status (%)	Never	36	56	78	<0.001
	Former	8	6	2	
	Current	56	39	21	
Physical activity (IPAQ) (%)	Inactive	8	9	9	0.41
	Minimally active	40	38	35	
	HEPA active	52	54	56	

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; SD: Standard deviation; HEPA: health-enhancing physical activity (i.e., vigorous activity at least 3 days a week achieving at least 1,500 metabolic equivalent (MET) minutes per week or activity on 7 days of the week, achieving at least 3000 MET minutes per week; IPAQ: International Physical Activity Questionnaire

[a]P-value from analysis of variance for continuous variable and a χ^2 test for categorical variables, 2 sided;

[b]Manual occupations are agricultural worker, factory work or sales and service; non-manual are administrator/manager, professional/technical, military/disciplined

Table 2: Characteristics by Aldehyde Dehydrogenase 2 *(ALDH2)* Genotype Among 2,786 Older Southern Chinese Women From the Guangzhou Biobank Cohort Study

		ALDH2 genotype (from rs671)			
		Two active alleles (GG) (n=1445)	One active allele (GA) (n=1107)	No active allele (AA) (n=234)	[a]P value
FEV_1 (L)	Mean (SD)	1.85 (0.4)	1.80 (0.4)	1.79 (0.4)	0.009
FVC (L)	Mean (SD)	2.31 (0.4)	2.26 (0.5)	2.25 (0.4)	0.02
Height (cm)	Mean (SD)	154.0 (5.2)	153.7 (5.5)	153.3 (5.4)	0.07
Age group (%) years	50-54	25	22	24	0.43
	55-59	32	34	30	
	60-64	20	19	23	
	65-69	13	12	15	
	70-74	8	10	6	
	75-79	2	2	2	
	80+	1	1	1	
Education (%)	Less than primary	10	11	12	0.53
	Primary	29	32	30	
	Junior middle	26	26	24	
	Senior middle	28	24	26	
	Junior college	5	6	6	
	College	2	2	3	
[b]Longest held occupation (%)	Manual	68	71	68	0.14
	Non-manual	20	20	22	
	Others	13	10	10	
Smoking status (%)	Never	97	98	98	0.89
	Former	1	1	1	
	Current	1	1	1	
Secondhand smoke exposure at home (%)	Yes	66	65	65	0.67
Secondhand smoke exposure at indoor work (%)	Yes	44	46	47	0.69
Drinking status (%)	Never	58	68	75	<0.001
	Former	6	3	3	
	Current	37	29	22	
Physical activity (IPAQ) (%)	Inactive	8	6	3	0.02
	Minimally active	27	29	35	
	HEPA active	66	65	62	

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity ; SD: Standard deviation; HEPA: health-enhancing physical activity (i.e., vigorous activity at least 3 days a week achieving at least 1,500 metabolic equivalent (MET) minutes per week or activity on 7 days of the week, achieving at least 3000 MET minutes per week; IPAQ: International Physical Activity Questionnaire

[a]P-value from analysis of variance for continuous variable and a χ^2 test for categorical variables, 2 sided;

[b]Manual occupations are agricultural worker, factory work or sales and service; non-manual are administrator/manager, professional/technical, military/disciplined

Table 3: [a]Adjusted Association of Aldehyde Dehydrogenase 2 *(ALDH2)* Genotypes With % Predicted Lung Function Among 5,641 Older Southern Chinese in the Guangzhou Biobank Cohort Study

	% predicted FEV_1				% predicted FVC			
	Model 1		Model 2		Model 1		Model 2	
Genotype	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Overall (n=5,641)								
GG	Reference		Reference		Reference		Reference	
GA	-1.52	-2.52 to -0.51	-1.07	-2.07 to -0.06	-1.25	-2.15 to -0.35	-0.95	-1.84 to -0.05
AA	-2.05	-3.85 to -0.26	-1.70	-3.48 to 0.08	-1.65	-3.25 to -0.04	-1.43	-3.03 to 0.16
AIC	48847.1		48571.7		47588.7		47316.2	
P for trend	0.001		0.01		0.003		0.02	
P for sex interaction	0.93		0.88		0.95		0.96	
Men (n=2,855)								
GG	Reference		Reference		Reference		Reference	
GA	-1.31	-2.82 to 0.20	-0.88	-2.42 to 0.65	-1.11	-2.43 to 0.23	-1.01	-2.37 to 0.35
AA	-2.28	-4.99 to 0.43	-1.87	-4.61 to 0.88	-1.82	-4.21 to 0.57	-1.64	-4.06 to 0.79
AIC	25111.7		25004.0		24378.6		24293.5	
P for trend	0.04		0.13		0.05		0.09	
Women (n=2,786)								
GG	Reference		Reference		Reference		Reference	
GA	-1.48	-2.77 to -0.18	-1.17	-2.46 to 0.13	-1.23	-2.43 to -0.03	-0.83	-2.01 to 0.35
AA	-1.77	-4.05 to 0.52	-1.37	-3.65 to 0.91	-1.44	-3.55 to 0.68	-1.12	-3.20 to 0.96
AIC	23547.3		23502.6		23112.7		22980.6	
P for trend	0.02		0.07		0.04		0.13	

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; AIC: Akaike Information Criterion

[a]Model 1 was unadjusted; Model 2 additionally adjusted for alcohol use, smoking, secondhand smoke exposure at home (cohabited with a smoker) and at work (indoor), education, occupation, recruitment phase and physical activity; P values were 2 sided

Table 4: [a]Adjusted Association of Alcohol Use With % Predicted Lung Function Among 5,641 Older Southern Chinese in the Guangzhou Biobank Cohort Study

	% predicted FEV_1				% predicted FVC			
	Model 1		Model 2		Model 1		Model 2	
Alcohol use	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Overall (n=5,641)								
Never	Reference							
Occasional	2.79	1.64 to 3.94	2.60	1.44 to 3.76	2.23	1.20 to 3.26	2.07	1.03 to 3.10
Moderate	1.95	0.04 to 3.85	1.56	-0.38 to 3.49	1.69	-0.02 to 3.40	1.35	-0.38 to 3.08
Heavy	3.35	0.74 to 5.96	2.77	0.12 to 5.42	1.73	-0.60 to 4.07	1.23	-1.15 to 3.60
Former	-0.10	-2.24 to 2.05	-0.39	-2.55 to 1.77	-0.44	-2.36 to 1.48	-0.69	-2.63 to 1.24
AIC	48573.9		48571.7		47318.0		47316.2	
P for sex interaction	0.08		0.08		0.09		0.08	
Men (n=2,855)								
Never	Reference		Reference		Reference		Reference	
Occasional	3.89	2.11 to 5.67	3.65	1.84 to 5.46	3.02	1.44 to 4.59	2.79	1.19 to 4.38
Moderate	1.43	-0.99 to 3.84	0.99	-1.49 to 3.47	1.06	-1.08 to 3.20	0.63	-1.57 to 2.82
Heavy	3.61	0.65 to 6.55	3.03	-0.02 to 6.08	1.58	-1.03 to 4.18	0.99	-1.70 to 3.68
Former	0.00	-3.04 to 3.04	-0.34	-3.42 to 2.73	-0.37	-3.06 to 2.32	-0.70	-3.42 to 2.01
AIC	25002.4		25004.0		24292.5		24293.5	
Women (n=2,786)								
Never	Reference		Reference		Reference		Reference	
Occasional	1.90	0.43 to 3.36	1.76	0.28 to 3.23	1.50	0.16 to 2.83	1.39	0.05 to 2.73
Moderate	5.20	1.74 to 8.66	4.94	1.47 to 8.41	4.44	1.29 to 7.59	4.24	1.08 to 7.40
Heavy	7.12	-2.70 to 16.92	6.58	-3.25 to 16.4	9.21	0.27 to 18.14	8.81	-0.13 to 17.8
Former	0.22	-2.81 to 3.25	-0.02	-3.06 to 3.02	-0.29	-3.05 to 2.47	-0.47	-3.24 to 2.30
AIC	23502.3		23502.6		22979.1		22980.6	

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; AIC: Akaike Information Criterion

[a]Model 1 was adjusted for smoking, secondhand smoke exposure at home (cohabited with a smoker) and at work (indoor), education, occupation, recruitment phase and physical activity; Model 2 additionally adjusted for aldehyde dehydrogenase 2 *(ALDH2)* genotypes; P values were 2 sided